HHS Public Access

Author manuscript

*Clin Lymphoma Myeloma Leuk*. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

*Clin Lymphoma Myeloma Leuk*. 2017 August ; 17(8): 464–470. doi:10.1016/j.clml.2017.03.299.

# Philadelphia Chromosome-like Acute Lymphoblastic Leukemia

**Ching-Hon Pui**[1,2,4], **Kathryn G. Roberts**[2,4], **Jun J. Yang**[3,4], and **Charles G. Mullighan**[2,4]

[1]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

[2]Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN

[3]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN

[4]Department of Hematological Malignancies Program, St. Jude Children's Research Hospital, Memphis, TN

## Abstract

Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) is a recently described B-cell precursor ALL with a gene expression profile and a high frequency of *IKZF1* gene alteration similar to that of Ph-positive ALL. Its prevalence is approximately 12% in children, 21% in adolescents (16 to 20 years of age) and 20% to 24% in older adults above the age of 40 years old, with a peak (27%) in young adults 21 to 39 years old. It occurs more often in males and patients with Down syndrome. Ph-like ALL is overrepresented in those with Hispanic ethnicity and is associated with inherited genetic variants in *GATA3* (rs3824662). It is a clinically and biologically heterogeneous subtype of B-ALL. While most patients with Ph-like ALL have positive minimal residual disease after remission induction and poor event-free survival, approximately 40% of pediatric patients responded well to chemotherapy and can be cured with relatively low intensity of treatment. The treatment outcome correlated negatively with increasing age at presentation. Ph-like ALL is characterized by a wide range of genetic alterations that dysregulate several cytokine receptor and kinase signaling pathways, including *CRLF2* rearrangement in half of the cases and translocation of non-receptor tyrosine kinases (predominantly ABL-class and Janus kinases). Patients with ABL-class fusions respond clinically to ABL1 tyrosine kinase inhibitors, whilst mutations activating the JAK-STAT pathway are amendable to treatment with JAK inhibitors *in vitro* or in preclinical models. Prospective studies are needed to determine if incorporation of tyrosine kinase inhibitor targeting kinase alterations into intensive chemotherapy regimens will improve outcome of patients with Ph-like ALL.

### Keywords

Acute lymphoblastic leukemia; Ph-like ALL; BCR-ABL-like; tyrosine kinase inhibitors

Address for correspondence: Ching-Hon Pui, MD, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, ching-hon.pui@stjude.org.



**Disclosure**: The authors declare that they have no competing interests.

## Introduction

Based on gene expression profiling studies of B-cell precursor ALL (B-ALL), Philadelphia chromosome (Ph)-like (also known as *BCR-ABL1*-like) acute lymphoblastic leukemia (ALL) was independently identified by two groups of investigators in 2009 – the Children's Oncology Group (COG)-TARGET-St Jude consortium and the Dutch Childhood Oncology Group.[1,2] This subtype of B-ALL has a gene expression profile similar to that of Ph-positive ALL but lacks the BCR-ABL1 fusion protein expressed from t(9;22)(q34.1;q11.2), and was associated with unfavorable clinical outcome when treated with conventional chemotherapy.[1,2] Like Ph-positive ALL,[3] Ph-like ALL cases also have a high frequency of genetic alterations of *IKZF1*, which encodes the lymphoid transcription factor Ikaros.[1,2] Such alterations are associated with poor outcome in both Ph-positive and Ph-negative ALL,[4] in part by dysregulating adhesion of and mislocalizing leukemic cells in the bone marrow niche.[5] All subsequent pediatric and adult studies have shown that this subtype of ALL is associated with dismal outcome,[6–13] with the exception of St. Jude Total Therapy Study XV which was the first clinical trial to use minimal residual disease (MRD) levels prospectively during and after remission induction therapy to guide risk-directed treatment which attenuated the poor prognosis of Ph-like ALL despite its association with high MRD levels[14] (Table 1). We here review the recent advances in the clinical and biologic studies which can be used to improve outcome of this high-risk genetic subtype of ALL.

## Definition

Unlike Ph-positive and other genetic subtypes of ALL classified by non-random chromosomal translocations or gene fusions, Ph-like ALL is defined by gene expression profile and represents a more genetically heterogeneous disease. In fact, the two initial gene expression signatures used to make the original discovery identify an overlapping, but not identical subset of cases.[1,2,15] The COG-TARGET-St Jude consortium first identified a subset of *IKZF1*-altered, high-risk B-ALL cases with a gene expression profile similar to Ph-positive ALL using Gene Set Enrichment Analysis,[1] and subsequently used prediction analysis of microarrays (PAM) of Affymetrix gene expression microarray data of high-risk B-ALL to identify 257 gene probe sets that defined Ph-positive and Ph-like cases.[16] Genetic alterations deregulating cytokine receptor and tyrosine kinase genes, and deletions or mutations of the lymphoid transcription factor gene *IKZF1* (encoding Ikaros) are a hallmark of the subtype defined by this classifier. By contrast, the signature of Den Boer et al.[2] was based on hierarchical clustering of 110 probe sets identified to predict other major pediatric ALL subtypes (T-cell, *ETV6-RUNX1*, high hyperdiploid, *TCF3-PBX1*, *MLL*-rearranged, and *BCR-ABL1*). Ph-like ALL defined by this signature had frequent deletions in B-cell development genes (e.g., *IKZF1*), dic(9;20), and intrachromosomal amplification of chromosome 21.[2,7,15] Both signatures identified molecularly distinct but overlapping groups of patients with poor prognosis, but shared only nine overlapping probe sets of 7 genes (*CCND2*, *SH3BP5*, *ABL1*, *SOCS2*, *DUSP6*, *LST1*, *EGFL7*).[15] Interestingly, tyrosine kinase fusion genes involving *ABL1*, *PDGFRB* and *JAK2* were only found in Ph-like ALL patients using the classifier of COG-TARGET-St Jude consortium.[15]

Subsequently, the COG have developed a targeted low density array that quantitates expression of 8–15 genes that are overexpressed in Ph-like ALL.[12] These probe sets, and the statistical algorithm used to convert raw gene expression data into a single numerical score predictive of Ph-like ALL were selected and derived using large cohorts of cases with comprehensive genomic characterization. Thus, different clustering, prediction and quantitative PCR approaches have been used that result in inconsistent predictions, and this may result in confusion regarding the optimal approach to identify patients with Ph-like ALL. It is emphasized that the most consistent, robust predictions are obtained when gene expression prediction approaches are trained and applied using data from the same center and technical platforms; and that the approaches used must be shown to sensitively and reproducibly identify all kinase-activating alterations in Ph-like ALL.

## Prevalence and Clinical Features

The prevalence of Ph-like ALL differs by age, gender, race, ethnicity, and National Cancer Institute (NCI)-defined risk groups. It comprises approximately 12% of children with B-cell precursor ALL (10% of NCI standard-risk and 13% to 14% of NCI high-risk BALL), 21% of adolescents 16 to 20 years old, 27% of young adults 21 to 39 years old, and 20% to 24% of older adults above 40 years old.[8,11–13] (Table 1) Compared to Ph-positive ALL, the prevalence of Ph-like ALL is 3 to 4 times more common in children and approximately the same as that in adults. A higher proportion of patients with Ph-like ALL are males compared to those with non-Ph-like B-ALL in both children and adults with a male-to-female ratio of 2:1 and 1.6:1, respectively.[8,12,14] Hispanic patients have been shown to have a higher prevalence of Ph-like ALL, with a particular preponderance of *CRLF2* rearrangements.[13,17] This is in part explained by the higher frequency of germline Ph-like ALL risk variant in *GATA3* (rs3824662) in Hispanics with Native American genetic ancestry.[18] This germline *GATA3* SNP was also associated with high MRD at the end of remission induction and increased risk of relapse, a finding consistent with ancestry-related disparities in ALL treatment outcomes.[19]

Studies of pediatric Ph-like ALL have been conducted largely in patients with high-risk ALL with one exception which was performed among consecutive patients treated in St. Jude Total XV study.[14] The St. Jude study clearly showed that none of cases with a Ph-like gene expression profile had t(1;19)/*TCF3-PBX1*, t(4;11)/*KMT2A-AFF1*, or t(12;21)/*ETV6-RUNX1*, but the proportion of hyperdiploidy with more than 50 chromosomes did not differ significantly between the 40 Ph-like ALL and the 304 non-Ph-like B-ALL patients.[14] In the St. Jude study, the median age and median presenting leukocyte count did not differ significantly between Ph-like and non-Ph-like patients and hence there was no significant difference in the distribution of NCI-defined risk groups (based on age and presenting leukocyte count).[14] Compared with non-Ph-like B-ALL, Ph-like ALL patients were more likely to be male, have Down syndrome, and have higher MRD during and after remission induction; because of the MRD results, significantly higher proportion of patients with Ph-like ALL received intensive post-remission treatment (60% vs. 41%).[14] In a recent large multi-center study of 798 adult patients with B-ALL, the 194 patients with Ph-like ALL were more likely to be male and have significantly higher median presenting leukocyte

count (56.6 vs. 26.8 × $10^9$/L) than those with non-Ph-like B-ALL (excluding Ph-positive and *KMT2A*-rearranged ALL).[12]

In virtually all pediatric and adult studies, Ph-like ALL was associated with increased MRD levels after remission induction and poor overall outcome (Table 1).[1,2,6–13] In fact, in each age group, patients with Ph-like ALL had inferior outcome as compared to those with non-Ph-like ALL. Of interest, in the St. Jude Total Therapy study XV which featured MRD-directed treatment, the 40 patients with Ph-like ALL and the other 304 non-Ph-like B-ALL patients had the same overall 5-year event-free survival (90%±4.7% vs. 88.4%±1.9%) and 5-year overall survival (92.5%±4.2% vs. 95.1%±1.3%).[14] There was no significant difference in outcome between the two groups of patients in each of the three risk groups based on the MRD levels, albeit higher proportion of Ph-like ALL patients underwent allogeneic transplant due to high level of MRD (≥1%) at the end of remission induction, as compared to patients with non-Ph-like B-ALL (15% vs. 5%).[14] Similar to Ph-positive ALL, the outcome of Ph-like ALL correlated negatively with increasing age: children fared better than adolescents who in turn have superior outcome than young adults, and older adults have the worst outcome.[8,12] (Table 1)

## Biologic Features and Genomic Landscape

In contrast to many ALL genetic subtypes which have a single founding chromosomal rearrangement that results in deregulated expression of an oncogene or expression of a fusion oncoprotein, genome and transcriptome sequencing studies have shown Ph-like ALL to have a complex genomic landscape with diverse genetic alterations that dysregulate several classes of cytokine receptors and tyrosine kinases (Figure 1).[20] Similar to Ph-positive ALL, a hallmark of Ph-like ALL is the high frequency of *IKZF1* alterations (70% to 80%) as compared to non-Ph-like ALL (15%).[8,12,20]

Several classes of kinase-activating alterations have been described. These include alterations activating JAK-STAT signaling (involving *CRLF2*, *JAK2*, *EPOR* and other genes in this pathway), ABL-class fusions (*ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*); Ras pathway mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*); and uncommon fusions (*NTRK3*, *PTK2B, BLNK*)[8,12,20] (Figure 1, Table 2). Only a small subset of patients did not have a kinase-activating alteration identified by transcriptome analysis.

The largest class of kinase-activating lesions are those resulting in activation of JAK-STAT signaling. Of these, the majority are rearrangements or point mutations of *CRLF2.* Approximately half the Ph-like cases harbor rearrangement of the cytokine receptor *CRLF2* (cytokine receptor like factor 2), either as a translocation to the immunoglobulin heavy chain enhancer region (*IGH-CRLF2*) or as a focal deletion resulting in the expression of *P2RY8-CRLF2* fusion transcript.[21,22] Both result in expression of full-length CRLF2 which heterodimerizes with interleukin 7 receptor alpha (IL7RA) to form the receptor for thymic stromal lymphopoietin (TSLP). Less frequently, sequence mutations of CRLF2 are present (most commonly p.Phe232Cys) that result in dimerization of CRLF2. Among childhood and adolescent patients with *CRLF2* rearrangement, approximately half have concomitant activating mutations of the Janus kinase genes, *JAK1* or *JAK2*, resulting in the activation of

JAK-STAT signaling.[21–23] In adults, the frequency of *JAK* mutations in patients with *CRLF2* rearrangement is lower, with a ratio of 1:4 with JAK wild-type (Figure 1). Mutations in *IL7R* and *SH2B3* have also been identified in patients with *CRLF2* alterations that lack *JAK* mutations, indicating these lesions may cooperate with *CRLF2* overexpression to induce leukemogenesis.[8]

Several other genetic alterations activate JAK-STAT signaling. These include rearrangements of *JAK2* and *EPOR* (encoding the erythropoietin receptor), which account for approximately 7% and 5% of Ph-like ALL cases, respectively.[12,20] At least 19 different *JAK2* fusions have been identified, each of which result in expression of a chimeric fusion gene with preservation of the JAK2 kinase domain. With our ongoing sequencing study, the prevalence of *JAK2* fusions is similar between the different age groups (Figure 1).[8,12]

Five types of *EPOR* rearrangements have been identified.[12,24] The most common involved juxtaposition or translocation of the *EPOR* gene to the enhancer regions of immunoglobulin heavy or kappa loci, leading to the deregulated expression of a truncated form of the *EPOR* gene that has been shown to drive leukemogenesis.[24] Less frequent mechanisms involve insertion and truncation of *EPOR* into the upstream region of *LAIR1* or the *THADA* loci. The frequency of *EPOR* rearrangements appear to be twofold higher in young adults (9%) compared to children and adolescents (5% and 3%, respectively), and less frequent in adults over the age of 40 (1%; Figure 1). *JAK2* rearrangements lead to constitutive activation of JAK-STAT signaling, whereas the *EPOR* rearrangements result in stabilized expression of the erythropoietin receptor on the surface of B-cells, with failure of receptor downregulation and heightened JAK-STAT signaling in response to ligand (EPO) stimulation. In both contexts, the abnormal JAK-STAT signaling can be abrogated by the use of JAK inhibitors such as ruxolitinib, as has been demonstrated *in vitro* in cell line models, and in preclinical xenograft models.[24–26]

An additional subset of Ph-like patients have a range of sequence mutations and DNA copy number alterations (but without rearrangements of kinase or cytokine receptor genes) that activate the JAK-STAT pathway (*JAK1*, *JAK3*, *IL7R, SH2B3, IL2RB, TYK2*). *SH2B3* (LNK) encodes a negative regulator of JAK-STAT, and deletion of this gene leads to activation of the JAK-STAT pathway. Collectively these alterations were approximately two fold higher in children (14%) compared to adolescents (5.0%), and adults (7.3%).[8,20] Notably, these cases with mutations/deletions activating JAK-STAT signaling that lack a kinase-activating rearrangement frequently have chromosomal rearrangements resulting in the formation of fusion oncoproteins involving transcription factor genes (*EBF1, PAX5, ETV6*) and/or epigenetic regulators (*CREBBP, SETD2, ASXL1*). In these cases, the kinase mutations are commonly multi-/sub-clonal, indicating they are secondary driving events arising after the founding chromosomal rearrangement. These cases also have a lower frequency of *IKZF1* alteration, and a lower Ph-like gene expression coefficient on TLDA prediction analysis, suggesting these may represent a distinct subset of Ph-like ALL.

Approximately 10% of the Ph-like patients (17% in children, 9% in adolescents, 10% young adults and 9% older adults) have ABL-class gene fusions.[8,12,20] The kinases that are rearranged in this subset of Ph-like ALL (ABL1, ABL2, CSF1R, PDGFRA, PDGFRB) are

termed “ABL-class” in view of the ability of ABL1 inhibitors such as imatinib and dasatinib to inhibit the downstream signaling induced by each of the chimeric fusion proteins.[8,25] Multiple fusion partners have been identified in each of the ABL-class genes, and in each instance the fusion involved the kinase as the downstream partner, thus preserving the kinase domain.[12,20]

Another 4% of Ph-like cases have mutations of genes (*KRAS*, *NRAS*, *NF1*, *PTPN11*, and *CBL1*) that activate Ras signaling;[12,20] however, it should be noted that these Ras-activating mutations can also observed in hyperdiploid, hypodiploid, *KMT2A*-rearranged, and relapsed ALL.[27–29] Finally, several other rare kinase alterations involving *NTRK3*, *BLNK*, *PTK2B* and *TYK2* have also been identified in Ph-like ALL.[8,12,20] While relatively rare, identification and modeling of these uncommon fusions is important as they are amenable to targeting with different TKI than JAK-STAT/ABL-class Ph-like ALL. Additional new rearrangements of other genes will most certainly be identified in future studies.

## Diagnostic Considerations

The heterogeneous genomic landscape and the diverse array of targetable kinase-activating lesions of Ph-like ALL have created a diagnostic dilemma and challenge for most hematopathologists and oncologists. Currently, pediatric study groups and centers have adopted different strategies to diagnose and to characterize Ph-like ALL based on the geographic structure of clinical trials, number of patients to be tested, availability of genome/transcriptome sequencing infrastructure, and clinical goal. Broadly, these approaches range between comprehensive sequencing of all patients at diagnosis irrespective of Ph-like status (the St Jude approach), to tiered algorithms that first identify Ph-like ALL using TaqMan low-density array screening followed by sequential genomic profiling (the COG approach), and focused fusion/gene panel testing. While each approach has its merits, the optimal strategy is critically dependent on the clinical requirement (e.g. identification of all Ph-like patients and comprehensive genomic characterization vs. identification of those with ABL-class lesions only).

The COG has established an algorithm to evaluate all newly diagnosed high-risk B-ALL.[30] They first use a validated Taqman low-density array card to screen for the Ph-like ALL gene signature.[31] Patients positive for Ph-like ALL (excluding *BCR-ABL1* or *ETV6-RUNX1* fusion-positive patients), are then stratified by CRLF2 expression. Those with high CRLF2 expression are tested for *CRLF2* rearrangement by fluorescence *in situ* hybridization and *JAK1*/*JAK2* mutation by Sanger sequencing. Patients with low CRLF2 expression are assayed for other kinase alterations by reverse transcription polymerase chain reaction (RT-PCR) and subsequent transcriptome sequencing if negative by PCR. Our recent study of adults also used a similar approach to define the frequency of Ph-like ALL and spectrum of kinase alterations in this population.[12] The United Kingdom Medical Research Council screens patients who have poor early treatment response as defined by induction failure, positive MRD on day 14 or persistent MRD at week 14 for ABL-class fusion.[32] Although it is effective for research, this approach may delay identification of patients with kinase lesion for treatment with tyrosine kinase inhibitor during remission induction. At St. Jude, we will complete RNA-seq within the first two weeks of remission induction so that most patients

with targetable fusion transcripts can be identified to receive tyrosine kinase inhibitor and attain a solid remission, and then complete whole genome and whole exome sequencing to identify full repertoire of kinase alterations by the end of remission induction (day 42).

Other approaches include digital molecular barcoding platform NanoString that can multiplex more than 200 different genetic alterations, or Capture-based RNA sequencing (e.g. Archer FusionPlex Oncology Research Kit; Foundation One Heme, Foundation Medicine).[12] One may also choose to perform fluorescence *in situ* hybridization to assess for break apart of key kinase genes, multiplex RT-PCR, or next-generation sequencing techniques in selected patients (e.g., those with high level of MRD after remission induction), with the ultimate goal to improve outcome by identifying targetable kinase lesions.

## Therapeutic Opportunities

The excellent overall 5-year event-free survival of 90.0%±4.7% achieved for Ph-like ALL patients in Total XV study[14] suggested that MRD-directed treatment should be applied to patients with Ph-like ALL. However, it should be noted that the underlying genomic alterations in our Ph-like ALL patients may be different to those reported for other high-risk cohorts, particularly with respect to the frequency of *CRLF2* rearrangements (28% in Total XV study compared to 50% in other series) which are associated with poor prognosis,[21,22] perhaps due to the reduced number of Hispanic patients treated at St. Jude. We observed a similar frequency of ABL-class fusions, but did not identify any JAK2 or EPOR rearrangements, which are also associated with a higher risk of relapse.[8] Nonetheless, we still observed higher MRD levels after remission induction in our Ph-like patients as compared to those of patients with non-Ph-like ALL. We attributed our success in treating Ph-like ALL patients to MRD-directed treatment such that poor responders received intensified treatment, including hematopoietic cell transplantation in 15% of the patients. It is also emphasized that 40% of patients treated on St Jude Total Therapy XV actually had low-risk leukemia based on negative MRD at the end of induction, and they had 5-year event-free survival of 100% despite receiving relatively low intensity of treatment. Notwithstanding this result, one third of the transplanted patients relapsed, and the addition of targeted therapy could have prevented relapse or spared some of them from transplantation.

Anecdotal reports have shown that patients with refractory Ph-like ALL harboring ABL-class fusion had sustained remission after ABL inhibitors.[8,32–34] Based on the recent improvement of outcome of Ph-positive ALL with the addition of an ABL inhibitor,[35,36] there is a strong rationale to conduct the same prospective studies in Ph-like ALL incorporating chemotherapy with appropriately targeted therapy based on the types of kinase lesions (Table 2). While ABL1-class and JAK-STAT alterations account for the majority of Ph-like ALL cases, there are several alterations involving kinases that are not inhibited by ABL-class nor JAK inhibitors (e.g. BLNK, NTRK3 and TYK2). Future studies are required to assess the potential for targeted inhibitors of these kinases in model systems and human leukemic cells.

## Conclusions and Future Perspective

Ph-like ALL is a newly described subtype of B-cell precursor ALL characterized by gene expression profile similar to that of Ph-positive ALL with frequent *IKZF1* alterations (70% to 80%) but lack *BCR-ABL1* fusion gene. The prevalence varies with age, from 12% in children to 21% in adolescents, 20% to 24% in older adults and as high as 27% in young adults. Even though Ph-like ALL is associated with poor outcome, given the heterogeneity of treatment response, we recommend MRD-directed treatment to avoid over- or under-treatment and to use available techniques, preferably next-generation sequencing platform, to screen for genetic lesions that are amendable to treatment with currently available tyrosine kinase inhibitors, such as ABL-class or JAK inhibitors. Global collaboration will be needed to determine the optimal treatment for patients with other rare kinase alterations, such as Ras, *NTRK3*, *PTK2B*, and *TYK2*. To this end, MEK inhibition has shown some promise in targeting downstream Ras pathway,[37] and the specific TRK inhibitor, LOXO-101, effectively inhibited the *ETV6-NTRK3* translocation in preclinical models.[38] Finally, future studies should also focus on the mechanism of drug resistance to kinase inhibitors so that therapeutic intervention can be developed. For example, retinoids and focal adhesion kinase inhibitors can potentiate the activity of dasatinib in mouse and human BCR-ABL1 ALL with *IKZF1* mutation,[5,39] and ponatinib induced a transient remission in a case with ABL1 kinase domain mutation T315I after initial response to dasatinib.[40]

## Acknowledgments

Supported in part by U.S. National Institutes of Health Grants Nos. CA21765, CA36401, CA145707, U01 GM115279, U10 CA180861, U01 CA176063, and HHSN261200800001E; American Society of Hematology Scholar Award, a Stand Up to Cancer Innovative Research Grant; a St Baldrick's Foundation Scholar Award; a Leukemia and Lymphoma Society Specialized Center of Research (SCOR) award; and American Lebanese Syrian Associated Charities of St Jude Children's Research Hospital

## References

1. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009; 360:470–80. [PubMed: 19129520]
2. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol. 2009; 10:125–34. [PubMed: 19138562]
3. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008; 453:110–4. [PubMed: 18408710]
4. Martinelli G, Iacobucci I, Storlazzi CT, et al. IKZF1 (Ikaros) deletions in BCR-ABL1-positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. J Clin Oncol. 2009; 27:5202–7. [PubMed: 19770381]
5. Churchman ML, Low J, Qu C, et al. Efficacy of Retinoids in IKZF1-Mutated BCR-ABL1 Acute Lymphoblastic Leukemia. Cancer Cell. 2015; 28:343–56. [PubMed: 26321221]
6. Loh ML, Zhang J, Harvey RC, et al. Tyrosine kinome sequencing of pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group TARGET Project. Blood. 2013; 121:485–8. [PubMed: 23212523]
7. van der Veer A, Waanders E, Pieters R, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood. 2013; 122:2622–9. [PubMed: 23974192]

8. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014; 371:1005–15. [PubMed: 25207766]
9. Boer JM, Koenders JE, van der Holt B, et al. Expression profiling of adult acute lymphoblastic leukemia identifies a BCR-ABL1-like subgroup characterized by high non-response and relapse rates. Haematologica. 2015; 100:e261–4. [PubMed: 25769542]
10. Herold T, Schneider S, Metzeler K, et al. Philadelphia chromosome-like acute lymphoblastic leukemia in adults have frequent IGH-CRLF2 and JAK2 mutations, persistence of minimal residual disease and poor prognosis. Haematologica. 2016 Aug 25.:pii. haematol.2015.136366. [Epub ahead of print].
11. Tasian SK, Hurtz C, Wertheim GB, et al. High incidence of philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) in older adults with B-ALL. Leukemia. 2016 Dec 9. [Epub ahead of print]. doi: 10.1038/leu.2016.375
12. Roberts KG, Gu Z, Payne-Turner D, et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. J Clin Oncol. 2016 Nov 21.:JCO2016690073. [Epub ahead of print].
13. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood. 2016 Dec 5.:pii. blood-2016-07-726588. [Epub ahead of print].
14. Roberts KG, Pei D, Campana D, et al. Outcomes of children with BCR-ABL1–like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. J Clin Oncol. 2014; 32:3012–20. [PubMed: 25049327]
15. Boer JM, Marchante JR, Evans WE, et al. BCR-ABL1-like cases in pediatric acute lymphoblastic leukemia: a comparison between DCOG/Erasmus MC and COG/St. Jude signatures. Haematologica. 2015; 100:e354–7. [PubMed: 26045294]
16. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012; 22:153–66. [PubMed: 22897847]
17. Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood. 2010; 115:5312–21. [PubMed: 20139093]
18. Perez-Andreu V, Roberts KG, Harvey RC, et al. Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. Nat Genet. 2013; 45:1494–8. [PubMed: 24141364]
19. Yang JJ, Cheng C, Devidas M, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. Nat Genet. 2011; 43:237–41. [PubMed: 21297632]
20. Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. Nat Rev Clin Oncol. 2015; 12:344–57. [PubMed: 25781572]
21. Russell LJ, Capasso M, Vater I, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood. 2009; 114:2688–98. [PubMed: 19641190]
22. Mullighan CG, Collins-Underwood JR, Phillips LA, et al. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet. 2009; 41:1243–6. [PubMed: 19838194]
23. Mullighan CG, Zhang J, Harvey RC, et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A. 2009; 106:9414–8. [PubMed: 19470474]
24. Iacobucci I, Li Y, Roberts KG, et al. Truncating Erythropoietin Receptor Rearrangements in Acute Lymphoblastic Leukemia. Cancer Cell. 2016; 29:186–200. [PubMed: 26859458]
25. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012; 22:153–66. [PubMed: 22897847]
26. Maude SL, Dolai S, Delgado-Martin C, et al. Efficacy of JAK/STAT pathway inhibition in murine xenograft models of early T-cell precursor (ETP) acute lymphoblastic leukemia. Blood. 2015; 125:1759–67. [PubMed: 25645356]

27. Wiemels JL, Kang M, Chang JS, et al. Backtracking RAS mutations in high hyperdiploid childhood acute lymphoblastic leukemia. Blood Cells Mol Dis. 2010; 45:186–91. [PubMed: 20688547]
28. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet. 2013; 45:242–52. [PubMed: 23334668]
29. Irving J, Matheson E, Minto L, et al. Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood. 2014; 124:3420–30. [PubMed: 25253770]
30. Tran TH, Loh ML. Ph-like acute lymphoblastic leukemia. Hematology Am Soc Hematol Edu Program. 2016; 2016:561–6.
31. Harvey RC, Mullighan CG, Wang X, et al. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. Blood. 2010; 116:4874–84. [PubMed: 20699438]
32. Schwab C, Ryan SL, Chilton L, et al. EBF1-PDGFRB fusion in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL): genetic profile and clinical implications. Blood. 2016; 127:2214–8. [PubMed: 26872634]
33. Weston BW, Hayden MA, Roberts KG, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. J Clin Oncol. 2013; 31:e413–6. [PubMed: 23835704]
34. Lengline E, Beldjord K, Dombret H, et al. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1-PDGFRB fusion. Haematologica. 2013; 98:e146–8. [PubMed: 24186319]
35. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia. 2014; 28:1467–71. [PubMed: 24441288]
36. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol. 2012; 13:936–45. [PubMed: 22898679]
37. Irving J, Matheson E, Minto L, et al. Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood. 2014; 124:3420–30. [PubMed: 25253770]
38. Roberts KG, Bridges O, Janke LJ, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101 in Acute Lymphoblastic Leukemia. Blood. 2016; 128:278.
39. Churchman ML, Evans K, Richmond J, et al. Synergism of FAK and tyrosine kinase inhibition in $Ph^+$ B-ALL. JCI Insight. 2016; 1(4):pii, e86082. Epub 2016 Apr 7.
40. Yeung DT, Moulton DJ, Heatley SL, et al. Relapse of BCR-ABL1-like ALL mediated by the ABL1 kinase domain mutation T315I following initial response to dasatinib treatment. Leukemia. 2015; 29:230–2. [PubMed: 25179732]

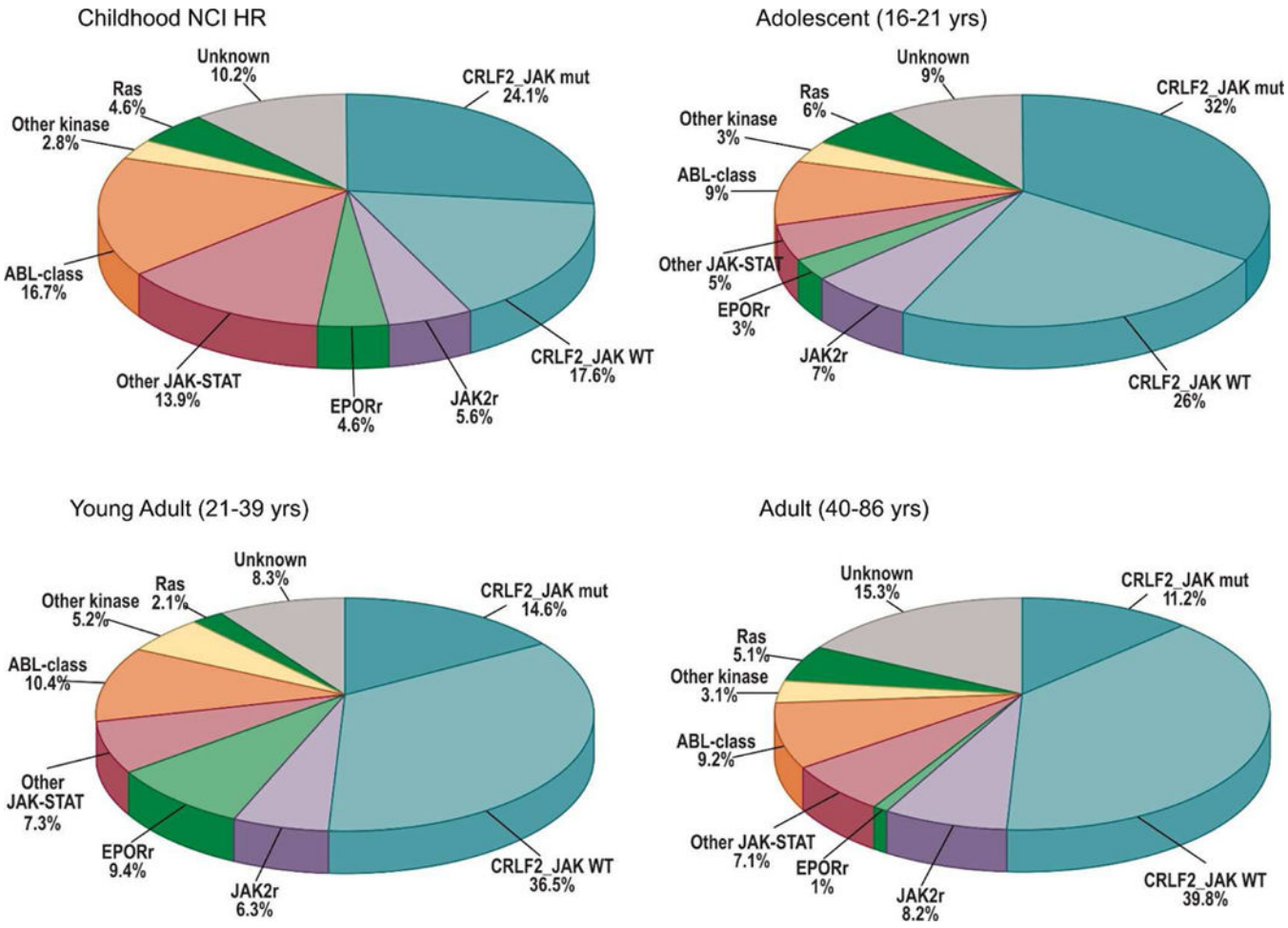


**Figure 1.**

Frequency of genetic subtypes in patients with Ph-like ALL by age group.[8,12,20] Combined prevalence of Ph-like ALL subtypes in (a) children, (b) adolescents, (c) young adults and (d) adults including *CRFL2*-rearranged *JAK2* mutant and *CRFL2*-rearranged *JAK2* wild-type; *ABL*-class rearrangements (*ABL1*, *ABL2*, *CSF1R, PDGFRA* and *PDGFRB*); *JAK2* and *EPOR* rearrangements, other mutations in JAK–STAT signaling (*IL7R*, *SH2B3*, *JAK1/3*, *TYK2*, *IL2RB* and *TSLP*); other kinase alterations (*FLT3*, *NTRK3*, *BLNK*, *PTK2B*), Ras mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*, *BRAF* and *CBL*) and unknown alterations.

**Table 1**

Prevalence and treatment outcome of Philadelphia chromosome-like ALL by age group

| Clinical Trial | Age (years) | Risk Group | Ph-like ALL Prevalence (%) No. | | Treatment Outcome | | Reference |
|---|---|---|---|---|---|---|---|
| P9906 | 1–18 | high-risk | 31 | 68 | 5-yr EFS | 25.9% ± 10% | Mullighan[1] |
| COALL 92/97 | 0–18 | all | 19 | 28 | 5-yr DFS | 59.5% | Den Boer[2] |
| DCOG-ALL-8/9 | 0–18 | all | 15 | 10 | 5-yr DFS | 57.1% | Den Boer[2] |
| AALL0232 | 1–18 | high-risk | 14 | 81 | 5-yr EFS | 62.6% ± 6.9% | Loh[6] |
| DCOG-ALL-8/9/10 | 1–18 | all | 16 | 94 | 5-yr CIR | 32% | van der Veer[7] |
| Multiple trials | | | | | | | Roberts[8] |
| | 1–15 | standard-risk | 10 | 33 | — | — | |
| | 1–15 | high-risk | 12.7 | 108 | 5-yr EFS | 58.2% ± 5.3% | |
| | 16–20 | all | 20.6 | 77 | 5-yr EFS | 41.0% ± 7.4% | |
| | 21–39 | all | 27.4 | 46 | 5-yr EFS | 24.1% ± 10.5% | |
| HOVON | 16–71 | all | 17 | 21 | 3-yr EFS | ~25% | Boer[9] |
| GMALL | 15–65 | all | 13 | 26 | 5-yr DFS | 24% | Herold[10] |
| University Pennsylvania | | | | | | | Tasian[11] |
| | 18–39 | all | 25.9 | 7 | — | — | |
| | 40–88 | all | 18.3 | 11 | — | — | |
| Multiple trials | | | | | | | Roberts[12] |
| | 21–39 | all | 27.9 | 96 | 5-yr EFS | 24.1% | |
| | 40–59 | all | 20.4 | 62 | 5-yr EFS | 21.4% | |
| | 60–86 | all | 24 | 36 | 3-yr EFS | 8% | |
| MD Anderson | 15–84 | a ll | 33.1 | 49 | 5-yr OS | 23% | Jain[13] |
| St. Jude Total XV | 1–18 | all | 11.6 | 40 | 5-yr EFS | 90.0% ± 4.7% | Roberts[14] |

Abbreviations: COALL = German Cooperative Acute Lymphoblastic Leukemia; DCOG = Dutch Childhood Oncology Group;

AALL = acute lymphoblastic leukemia trial; HOVON = Hematology-Oncology Foundation for Adults in the Netherlands;

EFS = event-free survival; DFS = disease-free survival; CIR = cumulative risk of relapse; OS=overall survival

## Table 2

Kinase rearrangements and therapeutic targets in Ph-like ALL *

| Kinase | T yrosine kinase inhibitor | Number of gene partners | Fusion partner genes |
|---|---|---|---|
| *ABL1* | Dasatinib | 12 | *CENPC, ETV6, FOXP1, LSM14, NUP214, NUP153, RCSD1, RANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1* |
| *ABL2* | Dasatinib | 3 | *PAG1, RCSD1, ZC3HAV1* |
| *CSF1R* | Dasatinib | 3 | *SSBP2, MEF2D, TBL1XR1* |
| *PDGFRB* | Dasatinib | 7 | *ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8* |
| *PDGFRA* | Dasatinib | 1 | *FIP1L1* |
| *CRLF2* | JAK2 inhibitor | 2 | *IGH, P2RY8* |
| *JAK2* | JAK2 inhibitor | 1 9 | *ATF7IP, BCR, EBF1, ETV6, PAX5, PCM1, PPFIBP1, RFX3, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274, GOLGA5, SMU1, HMBOX1, SNX29, ZNF340* |
| *EPOR* | JAK2 inhibitor | 4 | *IGH, IGK, LAIR1, THADA* |
| *TSLP* | JAK2 inhibitor | 1 | *IQGAP2* |
| *DGKH* | Unknown | 1 | *ZFAND3* |
| *IL2RB* | JAK1/JAK3 inhibitor | 1 | *MYH9* |
| *NTRK3* | TRK inhibitor | 1 | *ETV6* |
| *PTK2B* | FAK inhibitor | 3 | *KDM6A, STAG2, TMEM2* |
| *TYK2* | TYK2 inhibitor | 3 | *MYB, SMARCA4, ZNF340* |
| *FLT3* | FLT3 inhibitor | 1 | *ZMYM2* |
| *FGFR1* | Sorafenib/dasatinib | 1 | *BCR* |
| *BLNK* | ?SYK/MEKi | 1 | *DNTT* |

* Update of data from Roberts & Mullighan[20]